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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/444,281	11/19/99	BURIAN J	660081.411

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EXAMINER	
SCHNIZER, H	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/444,281	Applicant(s) BURIAN ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9 & 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Restriction/Election

1. Applicant's election without traverse of Group I, Claims 1-18 and 20 in Paper No. 10 is acknowledged.

Status of the Claims

2. The Amendment filed February 13, 2001 (Paper No. 10) has been entered. Non-elected Claims 19, and 21-28 have been cancelled. Therefore, elected Claims 1-18 and 20 are pending.

Drawings

3. The drawings filed 11/19/99 are objected to for reasons cited on the Form PTO 948.

Objections

4. In Claims 5 and 14, line 4, it appears that the phrase "having at least peptide" was intended to read "having at least one peptide".

5. In Claim 10, it appears that the phrase "wherein the number of anionic spacer peptides greater than..." was intended to read "wherein the number of anionic spacer peptides is greater than...".

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 5, 6, 7, 10, 11, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 5 and 14 are unclear as to how the anionic spacer and cationic peptide fit into the structure recited in claim 1. This ambiguity is further illustrated in the prior art rejection given below. For example, Claim 5 appears to indicate that the cationic peptide has "at least the structure (cleavage site)-(cationic peptide) whereas Claim 1 from which it depends appears to require more, (cationic peptide)-[(cleavage site)-(cationic peptide)]. Therefore, it appears that claim 5 is improperly dependent from Claim 1. Claims 6, 7, 10, and 11, dependent from Claim 5, fail to clarify this ambiguity. Clarification is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-18 and 20 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for the following:

1) expression cassettes comprising the structure (cationic peptide)-[(cleavage site)-(cationic peptide)]n, wherein n has a value of 1-4 or

2) expression cassettes comprising the structures and encoding the peptides disclosed in the specification.

However, the specification does not reasonably provide enablement for

1) expression cassettes comprising the structure (cationic peptide)-[(cleavage site)-cationic peptide)]$_n$ wherein n is between 1 and 100 (clm 1), 5 and 40 (clm 3) or wherein the fusion protein comprises from 4 to 40 (clm 8) or 3 to 15 (clm 9) cationic peptides, or

2) for expression cassettes comprising the structure (cationic peptide)-[(cleavage site)-cationic peptide)]$_n$ wherein n is between 1 and 100 and wherein the nucleic acid also encodes a carrier protein at the C-terminus (clm 2) or

3) an expression cassette wherein the nucleic acid encodes a fusion protein comprising a carrier protein, an anionic spacer with the structure (cleavage site)-(anionic spacer peptide), and a cationic peptide with the structure (cleavage site)-(cationic peptide) the carrier protein, the anionic spacer, and the cationic peptide can be in any order. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

11. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

12. Expression cassettes containing greater than 4 copies of cationic peptide are not enabled.

13. Claims 1, 3, 8, and 9 are drawn to expression cassettes encoding polypeptides containing 1-100 (clm 1), 5-40 (clm 3), 2-40 (clm 8), 3-15 (clm 9) cationic peptide repeats separated by cleavage sites. Claims 2, 4, 12, 13, 15-18, and 20 are dependent from these claims yet do not further limit the number of cationic peptide repeats. It appears that the polynucleotide constructs are to be used in high level expression of the cationic peptides. However, the prior art appears to provide evidence that expression of cationic peptides using expression cassettes that do not contain anionic peptide fusions have been unsuccessful in expressing the cationic peptides due to the large positive charges. For example, Hancock et al. (WO 96/28559, 1996; ref. AK of IDS of Paper No. 11) state that when sequences encoding cationic peptides are placed into expression vectors without an amino terminal sequence encoding an anionic carrier peptide, no peptide was observed upon expression (p. 6, lines 7-12). Moreover, Lee et al. (Protein Exp. & Purif. (1998) 12: 53-60; ref. BG of IDS of Paper No. 9) disclose expression cassettes that would meet the limitations of claims 1, 3, 4, 8, 9, 15-18, and 20 yet indicate that such an expression cassette failed to produce significant amounts of the cationic peptide (p. 56, Col. 2, lines 27 and Fig. 3B, lanes 4-6). Lee et al. teach the construction of an expression cassette that codes for buforin II (an antimicrobial cationic peptide) and contains two methionine codons flanking the buforin II gene. The methionine residues are intended for cleavage of the tandem multimers of buforin II with cyanogen bromide. Lee et al. indicate that clones containing 1, 2, 4, and 6 copies

of buforin II were poorly expressed and that this poor expression may be due to interference of transcription and translation by the strong positive charge of the resulting cationic peptides(see p. 56, col. 2, "Construction and Expression of the Buforin II Gene as Tandem Repeats"). In addition, Zhang et al. (Biochem. Biophys. Res. Comm. (1998) 247: 674-680; Ref. AP of IDS of Paper No. 11)also indicate that an indispensable element in recombinant cationic peptide expression is the anionic peptide (see p. 678, Col. 1, lines 1-5; and Table 2, constructs 5 and 15). Table 2 shows that expression constructs containing the α-helical peptide CEMA fused to the carrier protein Rep78 or fused to Rep21 and the cellulose binding domain did not successfully express the cationic peptide (Table I, constructs 5 and 15) whereas identical constructs having an anionic spacer peptide were used successfully in the production of the cationic peptide (see Table I, constructs 2 and 9). Therefore, it appears that the state of the prior art at the time of the invention was that cationic peptides could not be successfully expressed using expression constructs containing even just one cationic peptide repeat, in the absence of an anionic spacer.

14. The present invention appears to have been successful in expressing a cationic peptide without fusion to an anionic spacer, however, the greatest number of cationic peptide repeats allowable for successful expression seems to be four. The specification describes an expression construct containing a sequence encoding a cationic peptide derived from modifications of indolicidin (MBI-11) fused to CBD180 (cellulose binding domain) carrier protein. The specification indicates that high levels of gene expression were achieved with single and double copies of MBI-11. However, the specification

indicates that a dramatic decrease in expression was encountered when the number of genes encoding the cationic peptide exceeded three (see p. 26, lines 25-26 and Figure 3 and its figure legend on p. 7).

15. The specification does not provide any guidance as to what particular features of the disclosed constructs made them successful relative to the many failures of other constructs disclosed in the prior art. Therefore, it appears that the specification enables the use of expression constructs containing sequences shown to be successful in the specification. However, the specification does not enable the use of expression constructs containing greater than four copies of the cationic peptide or containing constructs other than those disclosed in the specification because one of skill in the art would not know what changes could be made and still maintain the success of high level expression. Given the state of the art at the time of the invention, and the lack of guidance in the specification regarding what features made the disclosed expression constructs successful in high level expression as opposed to the expression constructs of Lee et al. and Zhang et al. The skilled artisan would not know whether or how changing the amino acid sequence of the cationic peptide, the carrier protein would effect the expression or whether or how the steps in expression are the key to successful use of the claimed expression constructs, or both. Without such guidance, the experimentation is undue.

16. Disclosed order and relative number of components of expression cassette required.

17. Claims 5-7, 10, 11, and 14 are drawn to expression cassettes encoding fusion proteins with carrier proteins, anionic spacers, and cleavage sites yet the claims indicate that the number and positions of any of these components is unlimited. Such a claim is infinitely broad as there is no limitation on the carrier protein, anionic peptide or cationic peptide, or their position relative to each other. However, the art shows that the position of each component is an essential element to the success of using the expression cassettes in expressing cationic peptides. Zhang et al. state that, "specific sequences of the fusion partner and their positioning relative to each other and the peptide were crucial" (p. 678, Col. 2, lines 10-13). For example, Zhang et al. show that the anionic domain must be immediately upstream of the cationic domain (p. 678, Col. 2, lines 16-17; and Table 2). Zhang et al. do not provide any guidance as to why the order is important therefore, the construction of the expression cassettes that can be used successfully to produce cationic peptides appears to be unpredictable. The specification only provides guidance as to the success in using multidomain constructs wherein the cationic peptide is an indolicidin sequence, the carrier protein is a cellulose binding domain (the carrier protein), the anionic spacer peptide has the sequence of HEAEPEAEPIM(SEQ ID NO:27) and wherein these components are placed in a particular order: *(carrier)* -[(cationic peptide)-(anionic peptide)]$_n$-(cationic peptide)$_2$, wherein n=1-28 (cationic repeats=3-30), or *carrier*-[(cationic peptide)-(anionic peptide)]$_n$, wherein n=5, 10, and 15 (presence of a carrier does not appear to be required for successful expression). The specification does not provide any guidance as to whether any of the components can be placed at any other position and still achieve successful

expression. Therefore, in light of Zhang et al. showing that the order of components is critical to the success of using the expression cassettes, the unpredictability of what order or what combination of components would produce a successful expression cassette, and in light of the absence of any guidance in the specification as to the success of using expression cassettes other than those disclosed in the specification, it would require undue experimentation to successfully use expression cassettes containing components other than those disclosed in the specification and in the positioning disclosed in the specification.

18. Due to the large quantity of experimentation necessary to generate the infinite number of expression cassettes recited in the claims and possibly screen same for successful expression, the lack of direction/guidance presented in the specification regarding which structural features are required in order to achieve successful expression, the absence of working examples directed to cassettes other than those of the structures disclosed, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of placement of different components in different positions in an expression construct, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner. Such a contribution would involve the determination of what structural features of an expression cassette

expressing a cationic peptide are essential for successful expression of the cationic peptide. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

20. Claims 5-7, 10, and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhang et al. (Biochem. Biophys. Res. Comm. (1998) 247: 674-680; Ref. AP of IDS of Paper No. 11).

21. Zhang et al. teach a multidomain fusion protein expression cassette, comprising a promoter (T7 promoter, see p. 678, Col. 2, 4th paragraph) operably linked to a nucleic acid molecule which is expressed as an insoluble protein (p. 678, Col. 2, second line of last paragraph), wherein said nucleic acid molecule encodes a polypeptide comprising the structure (carrier protein)-(anionic peptide)-(cleavage site)-(cationic peptide) (see construct no. 1 in Table 2). Thus, the cleavage site is on the C-terminal side of the anionic peptide and the N-terminal side of the cationic peptide. The carrier protein is a truncated cellulose binding domain of less than 100 amino acids and is located at the N-

terminus (see construct 1 and Fig. 1, CBD_{syn}) . The anionic peptide is the anionic pre-pro domain of HNP-1(see abstract, line 20 and p. 678, Col. 1, line 6) and lacks a cysteine (see Figure 1, bottom sequence). The cationic peptide is an alpha helical cationic peptide CEMA (see abstract). The expression cassette contained a methionine cleavage site between the anionic peptide and the cationic peptide (p. 676, Col. 1, lines 1-4). The cationic peptide produced in the study of Zhang et al. has antimicrobial activity (p. 679, Col. 1, second full paragraph). Expression cassettes 1 and 17 in Table 2 of Zhang et al. represent two examples of expression cassettes wherein the number of anionic spacer peptides is greater than or the same as the number of cationic peptides. Thus, it appears that Zhang et al. meet all of the limitations of the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Holly Schnizer
July 25, 2001